Serrated Polyps: Why all the Recent Hype?

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Dr. Meguerian and Dr. Cortas have no conflict of interest
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- INTRODUCTION
- PATHOLOGY OF SERRATED LESIONS
- MOLECULAR FEATURES OF THE SERRATED PATHWAY
- EPIDEMIOLOGY OF SERRATED LESIONS
  - Risk factors for serrated lesions
  - Association between serrated lesions and cancer
- DETECTION OF SERRATED LESIONS
- RECOMMENDATIONS REGARDING REMOVAL OF SERRATED LESIONS
- SERRATED POLYPOSIS SYNDROME (SPS)
- POST-POLYPECTOMY SURVEILLANCE OF PATIENTS WITH SERRATED LESIONS
CRC incidence rates per 100,000 and rates of CRC screening in individuals older than age 50

## Association of Colonoscopy and Death From Colorectal Cancer

<table>
<thead>
<tr>
<th>Completeness of the Colonoscopy</th>
<th>All Cancer</th>
<th>Right – Sided Cancer</th>
<th>Left- Sided Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>0.63 ( 0.57 – 0.69)</td>
<td>0.99 ( 0.86 – 1.14)</td>
<td>0.33 ( 0.28 – 0.39)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0.91 (0.78 – 1.07)</td>
<td>1.35 ( 1.07 – 1.69)</td>
<td>0.63 ( 0.49 – 0.81)</td>
</tr>
</tbody>
</table>

Associations with Interval Cancers

A) Serrated associations
- Features of interval cancers
  - Proximal location
  - MSI positive
  - CIMP positive

B) Other associations
- Colonoscopy by non-GI doctors
- Doctors with low ADRs
- Low cecal intubation rates
- Low polypectomy rates
- Indication of FOBT vs screening
- Incomplete polypectomy

MSI = Microsatellite Instability
CIMP = CpG island methylator phenotype
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WHO pathological classification of serrated colorectal lesions

- Hyperplastic Polyps (HP)------------------------->75%
- Sessile Serrated Adenoma / Polyp (SSA/P)-----15-25%
  - With or without cytological dysplasia
- Traditional Serrated Adenoma (TSA)-----------<10%
Normal colonic mucosa
Hyperplastic Polyp
Agreement for pathologic interpretation of SSA/P vs HP

- SSA commonly read as HP
- TSA commonly read as TVA

Khalid et al. World J Gastroenterol 2009
- 3 Expert GI Pathologists
- Re-read 45 Proximal HP’s (>5 mm) --- 2001

Conclusion: 30-80% of the Proximal HPs re-read as SSP.
Kappas = 0.14 - 0.38 ---- MODERATE AGREEMENT

Glatz K et al. Am J Clin Pathol 2007;127:938-945
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# Colorectal Cancer – Molecular Basis

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Frequency</th>
<th>Genes</th>
<th>MSI</th>
<th>Precursor</th>
<th>Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN</td>
<td>65- 70%</td>
<td>APC K-ras p53</td>
<td>Yes</td>
<td>Adenoma</td>
<td>Slow</td>
</tr>
<tr>
<td>Lynch</td>
<td>3%</td>
<td>MLH1 MLH2 MLH6 PMS2</td>
<td>Yes</td>
<td>Adenoma</td>
<td>Fast</td>
</tr>
<tr>
<td>CIMP</td>
<td>30-35%</td>
<td>BRAF</td>
<td>Sometimes</td>
<td>Serrated</td>
<td>Can be Fast</td>
</tr>
</tbody>
</table>

CIMP = CpG island methylator phenotype  
CIN   = Chromosomal instability
MOLECULAR FEATURES OF THE SERRATED PATHWAY OF CARCINOGENESIS
CpG island methylation leads to gene silencing

A: The gene promoter and coding regions of an active gene are indicated in red and blue, respectively

B: The aberrant addition of methyl groups (CH3) to CpG sites in the promoter region interferes with gene transcription, resulting in silencing

Leggett et al. GASTROENTEROLOGY May 2010 Vol. 138, No. 6
MOLECULAR FEATURES OF THE SERRATED PATHWAY OF CARCINOGENESIS
Mutation of the Oncogenes *BRAF* and *KRAS*

Mutations in the oncogenes *KRAS* or *BRAF* result in uncontrolled cell proliferation.

Leggett at al. GASTROENTEROLOGY May 2010 Vol. 138, No. 6
A schematic representation of the putative development of (CIMP)-high colorectal cancers with MSI through a serrated pathway via methylation of the \textit{MLH1} gene.
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Prevalence of Sessile Serrated Adenoma

Retrospective
2005-2007
White Light
21K Colonoscopies

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean size of SSA</td>
<td>8.1 mm (range 2-40 mm)</td>
</tr>
<tr>
<td></td>
<td>≤ 5 mm (42%), ≤ 9 mm (69%)</td>
</tr>
<tr>
<td>Mean No. of SSAs per patient</td>
<td>3 (range 1-24)</td>
</tr>
<tr>
<td>Location of SSAs</td>
<td>51%: Cecum, ascending colon</td>
</tr>
<tr>
<td></td>
<td>49%: Remaining colon</td>
</tr>
<tr>
<td>Appearance</td>
<td>Flat or sessile (all polyps)</td>
</tr>
<tr>
<td>Synchronous polyps of other histology</td>
<td>Present in 87 (51%) patients</td>
</tr>
<tr>
<td></td>
<td>TA: 62 (49%)</td>
</tr>
<tr>
<td></td>
<td>TVA: 13 (10%)</td>
</tr>
<tr>
<td></td>
<td>HP: 50 (40%)</td>
</tr>
<tr>
<td>Synchronous adenocarcinoma</td>
<td>7 (4%), all in right side of the colon</td>
</tr>
</tbody>
</table>

PREVALENCE OF SSA / P = 3%
Prevalence of sessile serrated adenomas

Prospective Study
Magnifying Chromoendoscopy – Indigo Carmine
190 Patients -Consecutive Colonoscopies
5 months period

<table>
<thead>
<tr>
<th></th>
<th>Adenomas ( TA, TVA)</th>
<th>Hyperplastic</th>
<th>SSA / P</th>
<th>TSA</th>
<th>Mixed Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring et al. 2007</td>
<td>60%</td>
<td>29%</td>
<td>9%</td>
<td>0.7%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Prevalence of SSA / P = 9%

Risk factors for serrated lesions

**Serrated lesions**

- Cigarette smoking
- Alcohol intake
- Fiber intake
- Calcium intake
- NSAIDS
- Family history of CRC
- High body mass index

INCONSISTENT associations with distal serrated lesions
Association between serrated lesions and cancer

Pathology series ------ 2416 SSA:

- 14% demonstrated cytological dysplasia
- 1% showed cancer

The mean age:

- SSA 61 years
- SSA with LGD 66 years
- SSA with HGD 72 years
- SSA with Cancer 76 years

Message: SSA without Dysplasia --------------- Cancer

MEAN INTERVAL OF 15 YEARS

Association between serrated lesions and cancer

Sessile Serrated Adenoma (SSA / P) has been associated with:

1) Synchronous cancers (Esp. if SSA >1 cm & Proximal location)
   - CIMP-High
   - MSI
   - *BRAF* mutation

2) **MSI-High** cancers c/w MSI-Stable cancers.
3) Increased risk of **Metachronous** cancer

Multiplicity is associated with the serrated pathway

Messcik CA et al. Dis Colon Rectum 2009 ; 52 : 1535 – 41
Hiraoka S et al. Gastroenterology 2010 ; 139 : 1503 – 10
Nosho K et al. Gastroenterology 2009 ; 137 : 1609 – 20
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## Endoscopic and Clinical features of Serrated Lesions

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Mean Size</th>
<th>Prevalence</th>
<th>Shape</th>
<th>Distribution</th>
<th>Malignant Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic Polyp</td>
<td>Small, often ( \leq 5 ) mm</td>
<td>Very common</td>
<td>Sessile/Flat</td>
<td>Mostly Distal</td>
<td>Very Low</td>
</tr>
</tbody>
</table>
A morphologic analysis of sessile serrated polyps observed during routine colonoscopy

Tadepallli US et al. Gastrointest Endosc 2011; 74: 1360 – 8
A morphologic analysis of sessile serrated polyps observed during routine colonoscopy

Tadepalli US et al. Gastrointest Endosc 2011; 74: 1360 – 8
Typical sessile lesion with mucous coat, benign crypt pattern, indistinct edges
The mucus looks red under NBI
No mucus = hard to see, easy to miss
Variable detection of adenomas among GI docs

<table>
<thead>
<tr>
<th></th>
<th>Number of doctors</th>
<th>Lowest ADR</th>
<th>Highest ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barclay et al.</td>
<td>12</td>
<td>9.4%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>9</td>
<td>15.5%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Imperiale et al.</td>
<td>25</td>
<td>7%</td>
<td>44%</td>
</tr>
<tr>
<td>Shaukat et al.</td>
<td>51</td>
<td>10%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Barclay RL et al. NEJM 2006 Dec 14;355(24):2533-41
Imperiale et al. GIE 2009 Jun;69(7):1288-95
Shaukat A et al. CGH 2009 Dec;7(12):1335-40
Variable detection of proximal colon serrated lesions among GI docs

<table>
<thead>
<tr>
<th>Number of Doctors</th>
<th>Lowest Proximal Colon Serrated lesion Detection rate</th>
<th>Highest proximal colon serrated lesion detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetzel et al.</td>
<td>13</td>
<td>1.1%</td>
</tr>
<tr>
<td>Kahi et al.</td>
<td>15</td>
<td>1%</td>
</tr>
</tbody>
</table>

Hetzel JT et al. Am J Gastro 2010 Dec;105(12):2656-64
Kahi CJ et al CGH 2011;9:42–46
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RECOMMENDATIONS REGARDING REMOVAL OF SERRATED LESIONS

- Complete removal of all serrated lesions should be performed except for diminutive sigmoid or rectal lesions.

- Multiple diminutive ($\leq 5$ mm) serrated appearing lesions in rectum/sigmoid should be randomly sampled for histology.

- 3 issues that can make endoscopic resection of serrated lesions difficult are shared with adenomas:
  - Size, Shape, and Location.

- Identifying the borders of the lesion can be very challenging.
  - Narrow band imaging
  - Surface dye-spraying
  - Submucosal injection of fluid containing a contrast agent.

Incomplete Polyp Resection During Colonoscopy—Results of the Complete Adenoma Resection (CARE) Study

Prospective
1400 patients

Incomplete Adenoma Resection by Histology

<table>
<thead>
<tr>
<th>Polyp Histology</th>
<th>Incomplete Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomatous polyps (n=346)</td>
<td>35 (10.1%)</td>
</tr>
<tr>
<td>Tubular adenomas (n=266)</td>
<td>20 (7.5%)</td>
</tr>
<tr>
<td>TVA/Villous adenoma (n=26)</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Sessile serrated adenoma (n=42)</td>
<td>13 (31.0%)</td>
</tr>
<tr>
<td>5-9mm</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>10-20mm</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>HGD/Cancer (n=12)</td>
<td>0</td>
</tr>
</tbody>
</table>

Serrated adenomatous polyps vs conventional adenomas:
RR 3.74 (95% CI 2.04-6.84)

Pohl E et al Gastroenterology 2012 Sep 25
RECOMMENDATIONS REGARDING REMOVAL OF SERRATED LESIONS

- Lesions <1cm can be resected with or without electrocautery

- Cold snaring >>>>>> Piecemeal resection using forceps.
  - Should include a narrow margin of normal mucosa

- Submucosal injection prevents mucosal “wrinkling” that facilitates snaring

- If piecemeal technique ---- Follow-up 3-6 months

- Surgical resection indicated:
  - Cannot be endoscopically excised
  - Numerous large serrated lesions in proximal colon.

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SERRATED POLYPOSION SYNDROME (SPS)

**WHO criteria** define the syndrome by **any one** of the following conditions:

(i) At least 5 serrated polyps proximal to the sigmoid colon with 2 or more of these being > 10 mm

OR

(ii) Any number of serrated polyps proximal to the sigmoid colon in an individual who has a **first-degree relative with SPS**

OR

(iii) > 20 serrated polyps of any size, distributed throughout the colon.
SERRATED POLYPOSIOS SYNDROME (SPS)

- Equal gender distribution
- Median age at diagnosis 44 – 62 years
- Substantial phenotypic diversity
- Most cases are sporadic
- Felt to be an indication of “methylator milieu”
- Exact risk of CRC unknown
SERRATED POLYPOSIS SYNDROME (SPS) Management

A. Indications for surgery:
   - CRC
   - When size and/or number of polyps makes endoscopic control impossible
   - Most common operations: (Extended right hemicolecetomy and Subtotal Colectomy

B. Annual colonoscopy

C. First degree relatives of patients with SPS may have an increased risk of CRC.
   \[ RR = 5.4 \]
   - Recommend screening colonoscopy every 5 years (or sooner if polyps) starting at age 40 or 10 years younger than age at diagnosis of youngest affected relative
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Recommendations
Post-Polypectomy Surveillance

Expert opinion

Effective polyp detection and resection—KEY!

The risk of developing CRC through the Serrated Pathway:

### Consensus opinion surveillance intervals after endoscopic resection of serrated lesions

<table>
<thead>
<tr>
<th>Histology</th>
<th>Size</th>
<th>Number</th>
<th>Location</th>
<th>Interval in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>&lt;10mm</td>
<td>Any number&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rectosigmoid</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>HP</td>
<td>≤5mm</td>
<td>≤3</td>
<td>Proximal to sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>HP</td>
<td>Any</td>
<td>≥4</td>
<td>Proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>HP</td>
<td>&gt;5mm</td>
<td>≥1</td>
<td>Proximal to sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10mm</td>
<td>&lt;3</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>≥10mm</td>
<td>1</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10mm</td>
<td>≥3</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSA/P</td>
<td>≥10mm</td>
<td>≥2</td>
<td>Any</td>
<td>1–3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>SSA/P w/dysplasia</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td>1–3&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Reasons for More Aggressive Surveillance

- Missed serrated lesions are felt to be an important contributor to interval cancers

- High variability in detection, so closer intervals to compensate for increased missing of serrated lesions

- Insufficient data about effectiveness of endoscopic resection of these lesions.
  - Can be difficult due to indiscrete borders and very flat shape.
Conclusions

- SSA/P and TSA are pre-malignant lesions
- Most large proximal colon serrated lesions are SSA/Ps
- Remove all the serrated lesions proximal to the sigmoid and all those > 5 mm in distal colon
- Follow-up is closer for:
  - SSA/P or TSA
  - Large size
  - Increased numbers of proximal lesions
Conclusions

- SSA/P is the main precursor of CIMP-high CRC
- Variability in detection; Measure your ADR
- No reliable way to distinguish HP from SSA/P endoscopically right now
- Agreement for pathologists distinguishing HP from SSA/P is moderate
- SSA/P with cytological dysplasia is dangerous